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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/306,333	05/06/99	VIJG J	VB

EXAMINER	
SOUAYA,J	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

1- File Copy

PTO-90C (Rev 11/00)

Office Action Summary

Application No.	Applicant(s)
09/306,333	Jan Vijg
Examiner	**Art Unit**
Jehanne Souaya	1655

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 8, 2001* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *4-11* is/are pending in the application.

4a) Of the above, claim(s) *7-9* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *4-6, 10, and 11* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☒ Claims *4-11* are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. Currently, claims 4-11 are pending in the instant application. Claims 7-9 have been withdrawn from consideration as being drawn to non-elected subject matter (see restriction requirement below). All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. Any rejections not reiterated are hereby withdrawn. The following rejections are either newly applied or are reiterated. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restriction

3. Restriction to one of the following inventions is required under 35 U.S.C. 121: Claims 10-11 are linking and will be examined with either Group I or Group II to the extent that they are drawn to the subject matter of Group I or Group II.

I. Claims 4-6, drawn to BRCA1 oligonucleotides, classified in class 536, subclass 23.1.

II. Claims 7-9, drawn to hMLH1 oligonucleotides, classified in class 536, subclass 23.1.

4. The inventions are distinct, each from the other because of the following reasons: The oligonucleotides of Groups I and II are drawn to different nucleic acids that encode different proteins with different structures and functions. These proteins and the nucleic acids that encode them are unobvious over one another.

5. Because these inventions are distinct for the reasons given above and the search required for Group I is not required for Group II, restriction for examination purposes as indicated is proper.

6. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, restriction for examination purposes as indicated is proper.

7. During a telephone conversation with Robert H. Rines a provisional election was made without traverse to prosecute the invention of Group I, claims 4-6 and claims 10-11 drawn to a method of detecting mutations in the BRCA1 gene. Affirmation of this election must be made by applicant in replying to this Office action. Claims 7-9 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 4-6 and 10-11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4-6 and 10-11 are indefinite as it cannot be determined which primers are paired in table 4 as table 4 also contains a column for "clamping sequences". With respect to claims 10 and 11, it cannot be determined which primers from table 1 are to be used with the primers from table 4. Furthermore, it cannot be determined if primers from table 4 are to be paired with primers from table 1?

Claim 10 is indefinite in the recitation of "substantially" in line 6 as it cannot be determined which primers from table 4 are "substantial" to the method of claim 10.

Claim 10 is indefinite as it cannot be determined how the first set of amplification products are different from the second set of amplification. The claim does not make clear how to "provide a second set of amplification products". Furthermore, the recitation of "this short distance PCR" appears to lack sufficient antecedent basis as it cannot be determined which "short distance PCR" the claim refers to. Is it the same as the short distance multiplex PCR which the first set of amplification products are subject to?

Specification

10. The amendment filed October 25, 2000 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: SEQ ID NOS 121 and 122 were not present in the original specification.

Applicant is required to cancel the new matter in the reply to this Office action.

Maintained Rejections

11. Claims 4-6 and 10-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vijg, Jan (WO 96/39535) in view of Vijg et al (Vijg II, US Patent 6,007,231), Park et al (US Patent 5,948,697) and Liskay et al (US Patent 5,922,855) .

Vijg teaches a method for diagnostic testing of DNA using PCR amplification followed by electrophoretic separation of the resulting fragments to detect possible gene variants of mutational defects (see abstract), specifically in the retinoblastoma gene. Vijg teaches that with the method, it is possible to test individual at any time for inherited gene-encoded predispositions to disease, including late onset diseases such as cancers and neurodegenerative diseases (see p. 3, lines 1-8). The method taught by Vijg comprises amplifying regions of target DNA, usually protein coding regions (exons), by PCR (see p. 6, lines 20-23) using primers which have been positioned to cover

the exons. Vijg teaches that these amplification reactions are conducted separately, eg., if 27 exons in a gene are being analyzed, then 27 separate PCR reactions must be conducted, but also teaches that it is usually possible to conduct a few PCR reactions together in one tube (see p. 7, first para). Vijg then teaches that primers for short PCR are positioned such that a) the desired target sequences should be covered by amplicons of between 100 and 600 bp, b) amplicons should have optimal melting behavior, ie: consist of one lowest melting domain in addition to the GC-clamp attached to one of the primers, c) optimal amplicon distribution over a 2D gel, and d) similar reaction kinetics (See table 1, p. 13). Vijg then teaches that the PCR conditions are set up separately for each primer set with the long-PCR products as template for the short PCR and that multiplex co-amplification conditions are developed by grouping primer sets and adjusting reaction components. After the PCR, Vijg teaches that the mixture of fragments are subjected to 2-D electrophoresis in a denaturing gradient gel(see p. 16, lines 16-20).

Although Vijg does not teach testing gene sequences of the BRCAI gene, Vijg does teach the use of the method to generally detect sequence mutations in any gene, provided the nucleotide sequence of the gene is known, and specifically teaches analyzing the retinoblastoma gene. The BRCAI gene sequence was well known in the art at the time of the invention, as was the link between mutations in this gene in different types of cancer (BRCAI in breast and ovarian cancer). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to use the method taught by Vijg to detect mutations in the BRCAI gene as Vijg teaches the usefulness of the method in detecting inherited gene-encoded predispositions

to disease, including late onset diseases such as cancers and neurodegenerative diseases. The ordinary artisan would have been motivated to use the method taught by Vijg to detect mutations in BRCAI as both Liskay et al and Park et al teach mutations in the BRCAI gene and its link to cancer. The ordinary artisan would have had a reasonable expectation of success that using the method taught by Vijg, primers could be generated that would successfully amplify the necessary coding regions of both the BRCAI gene and provide characteristic 2-D spot patterns for certain mutations as Vijg and Vijg II both teach in extensive detail (see pp 7-10, 18-19 of Vijg; and col.2, col.6, col.9, and claim 1 of Vijg II) how to prepare primers that would be successful in the method taught by Vijg given a known gene sequence.

Response to Arguments

All the amendments, arguments and Declaration have been thoroughly reviewed but were found unpersuasive. With respect to tables 1-4, as discussed in the 112/2nd rejection above, it cannot be determined which sequences are to be paired, especially as table 4 contains "clamping" oligonucleotides. The response and the declaration traverse that in addition to requiring the splitting of the BRCA1 gene into fragments, it was necessary for the BRCA1 gene to depart from the prior Vijg concept of a single stranded clamp bar primer pair and to provide instead clamps of variable sequence and links to induce a stable melting domain. This argument has been thoroughly reviewed but was found unpersuasive. With regard to the need to split the BRCA1 gene into fragments, the ordinary artisan would have been motivated to do so as the BRCA1 gene

is larger than the RB1 gene, and as the detection method of Vijg involves electrophoresis, the ordinary artisan would have known that smaller amplification products would have improved clarity and resolution in gel electrophoresis. Furthermore, the claims are drawn to using primer pairs from table 4, but it cannot be determined which primer pairs are being used. With respect to using clamping and linking sequences, the claims are not drawn to such a limitation. Although these constitute unexpected results, the claims are not drawn to such. It is further noted that clamping sequences SEQ ID NOS 121 and 122 do not appear to have been disclosed in the original specification.

Conclusion

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. No claims are allowable.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Souaya whose telephone number is (703)308-6565. The examiner can normally be reached Monday-Thursday from 7:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Lisa B. Arthur

LISA B. ARTHUR
PRIMARY EXAMINER
GROUP 1800 1600

Jehanne Souaya

Jehanne Souaya
Patent examiner
July 27, 2001